Improving the Accuracy of fMRI and fcMRI Analysis by Accounting for Spatiotemporal Processing Induced Correlations

M. Muge Karaman[1]

Department of Mathematics, Statistics, and Computer Science
Marquette University, Milwaukee, WI

meryem.karaman@marquette.edu

Joint with Daniel B. Rowe[1,2] and Andrew S. Nencka[2]

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Boston, MA

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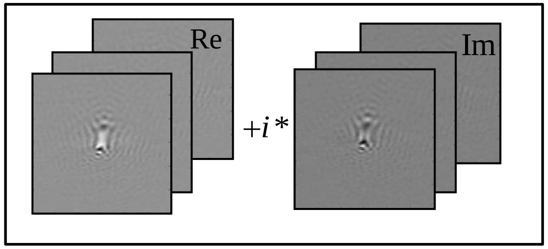
1 MARQUETTE

2 MEDICAL COLLEGE OF WISCONSIN

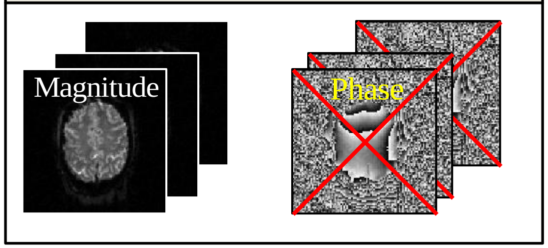
Examining the Statistical Effects of Spatiotemporal Processing

Experimental Design

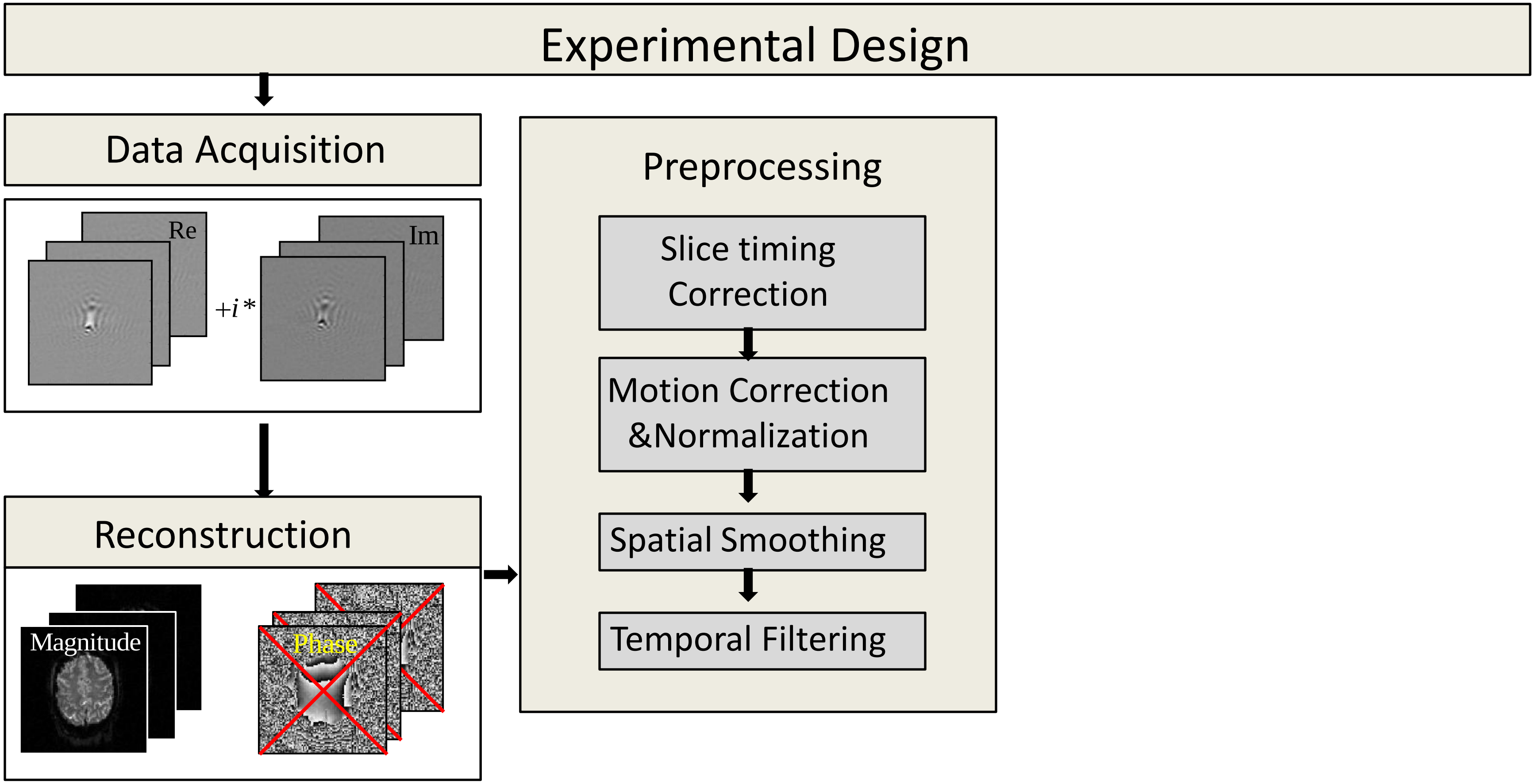
Data Acquisition



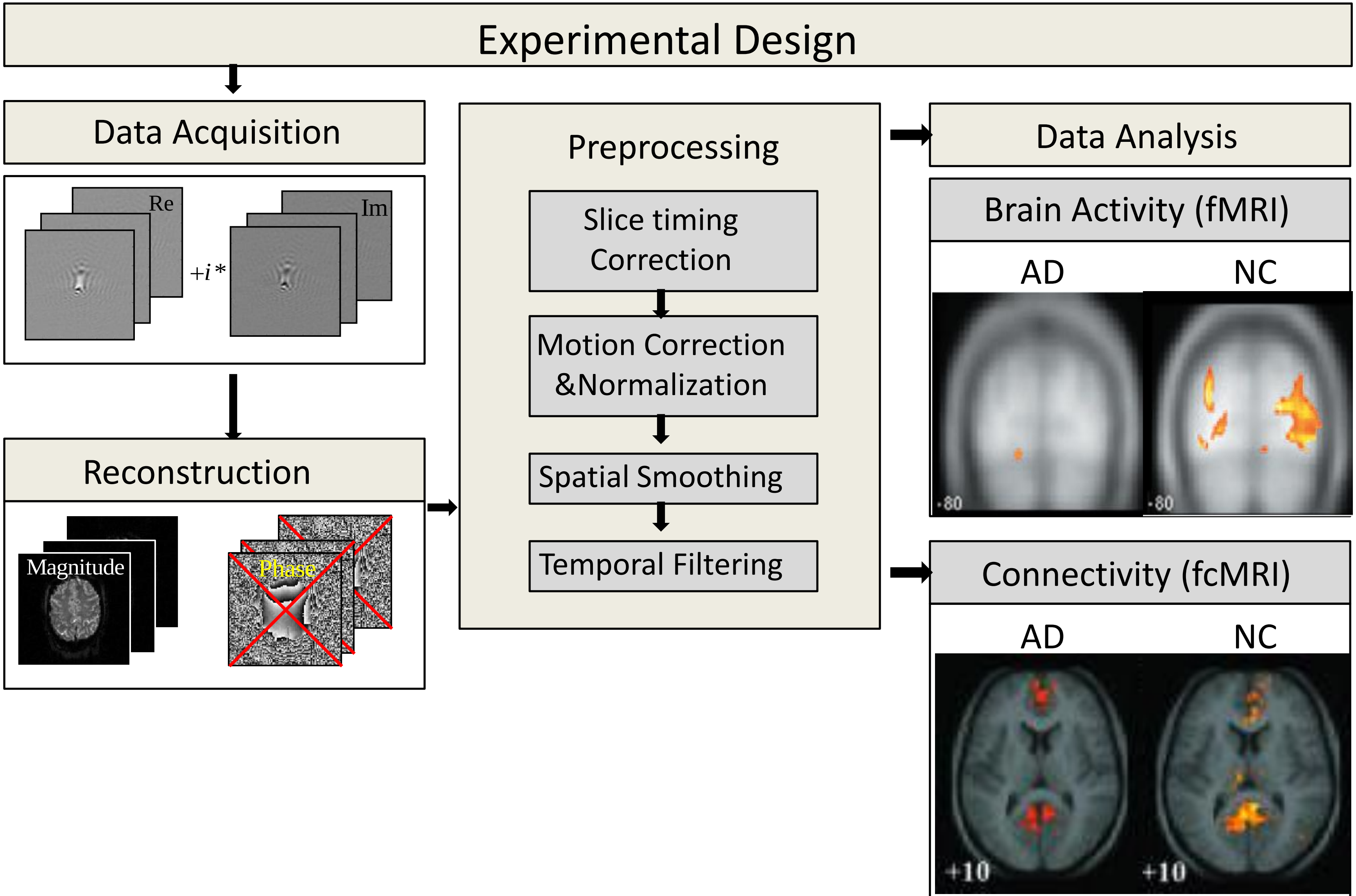
Reconstruction



Examining the Statistical Effects of Spatiotemporal Processing

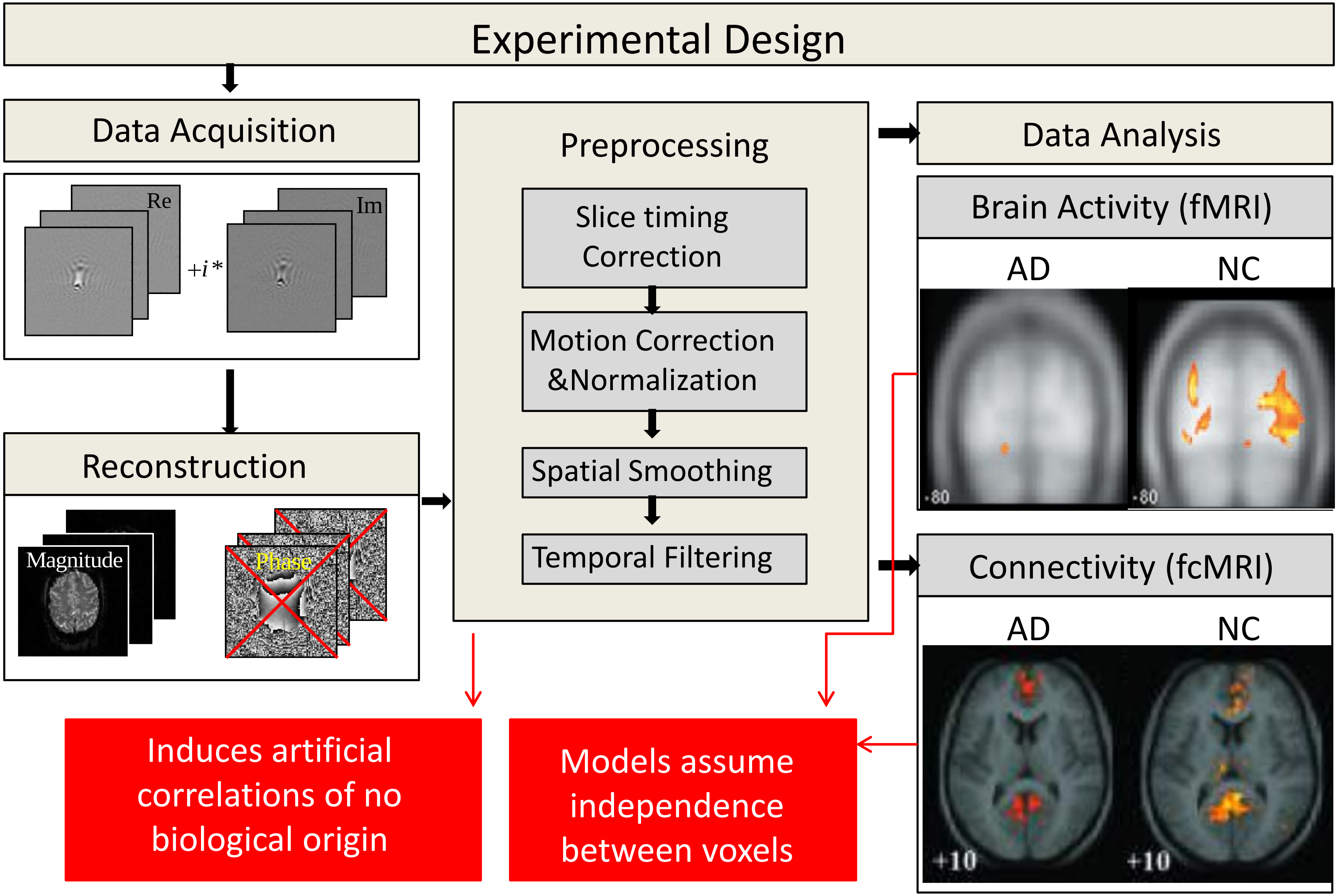


Examining the Statistical Effects of Spatiotemporal Processing



1) Golby et al.: Brain 128: 773–787, 2005. 2) Greicius et al.: Proc Natl. Acad. Sci. U S A, 101(13): 4637–4642, 2004.

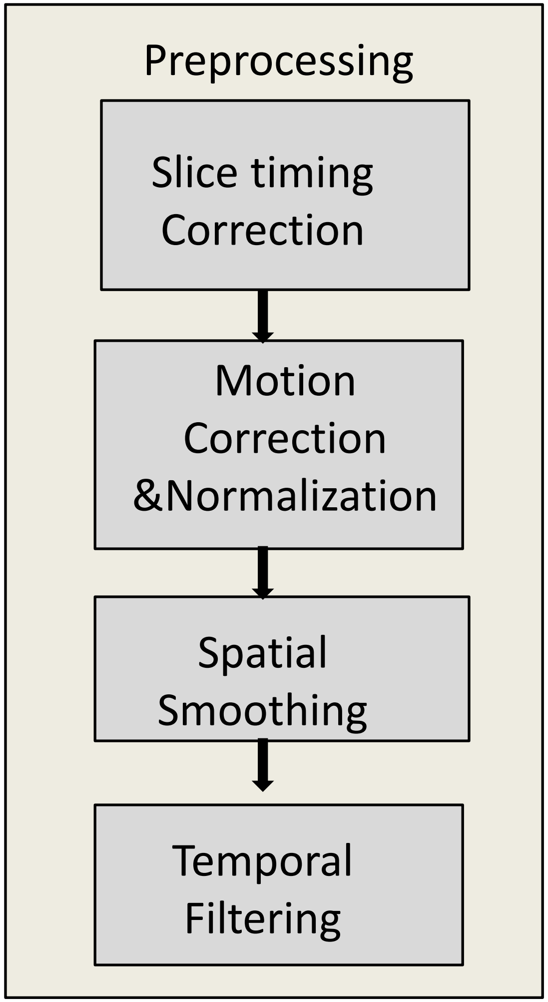
Examining the Statistical Effects of Spatiotemporal Processing



1) Golby et al.: Brain 128: 773–787, 2005. 2) Greicius et al.: Proc Natl. Acad. Sci. U S A, 101(13): 4637–4642, 2004.

Examining the Statistical Effects of Spatiotemporal Processing

Our Approach:



Examining the Statistical Effects of Spatiotemporal Processing

Our Approach:

Preprocessing

Slice timing Correction

↓

Motion Correction &Normalization

↓

Spatial Smoothing

↓

Temporal Filtering

→

Perform
- Image reconstruction
- Spatial Processing
- Temporal Processing

through ***linear operators***

↓

Analytically derive the ***exact*** noise properties of the processed data,

specifically the ***induced correlations by processing,*** Σ.

Examining the Statistical Effects of Spatiotemporal Processing

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through ***linear operators***

Analytically derive the ***exact*** noise properties of the processed data,

specifically the ***induced correlations by processing,*** **Σ.**

Data Analysis

Brain Activity (fMRI)

Expand the current fMRI activation model to incorporate **Σ.**

Connectivity (fcMRI)

Utilize the computed, **Σ.**

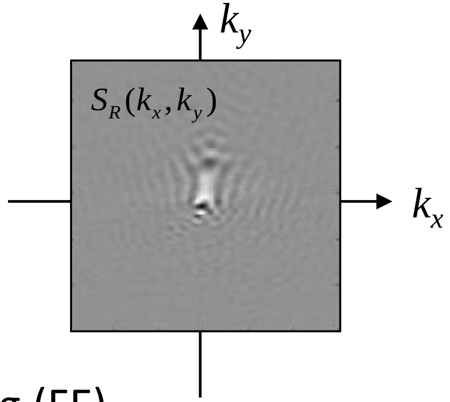
Background – Complex-valued image reconstruction

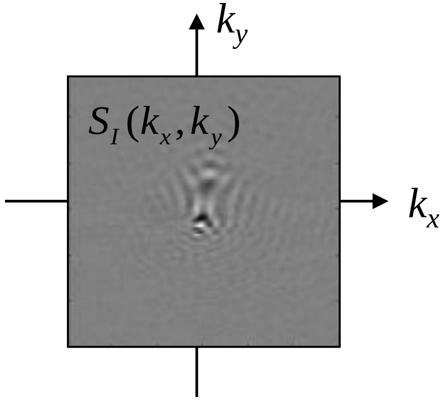
- In MRI, magnetic field gradients Fourier encode the complex-valued spatial frequencies of an object.

Physical object

Fourier encoding (FE)

FT





$S(k_x,k_y)$: acquired k-space signal

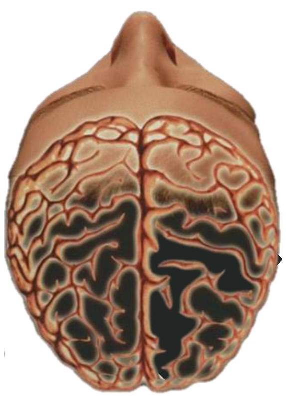
Frequency space (k-space)

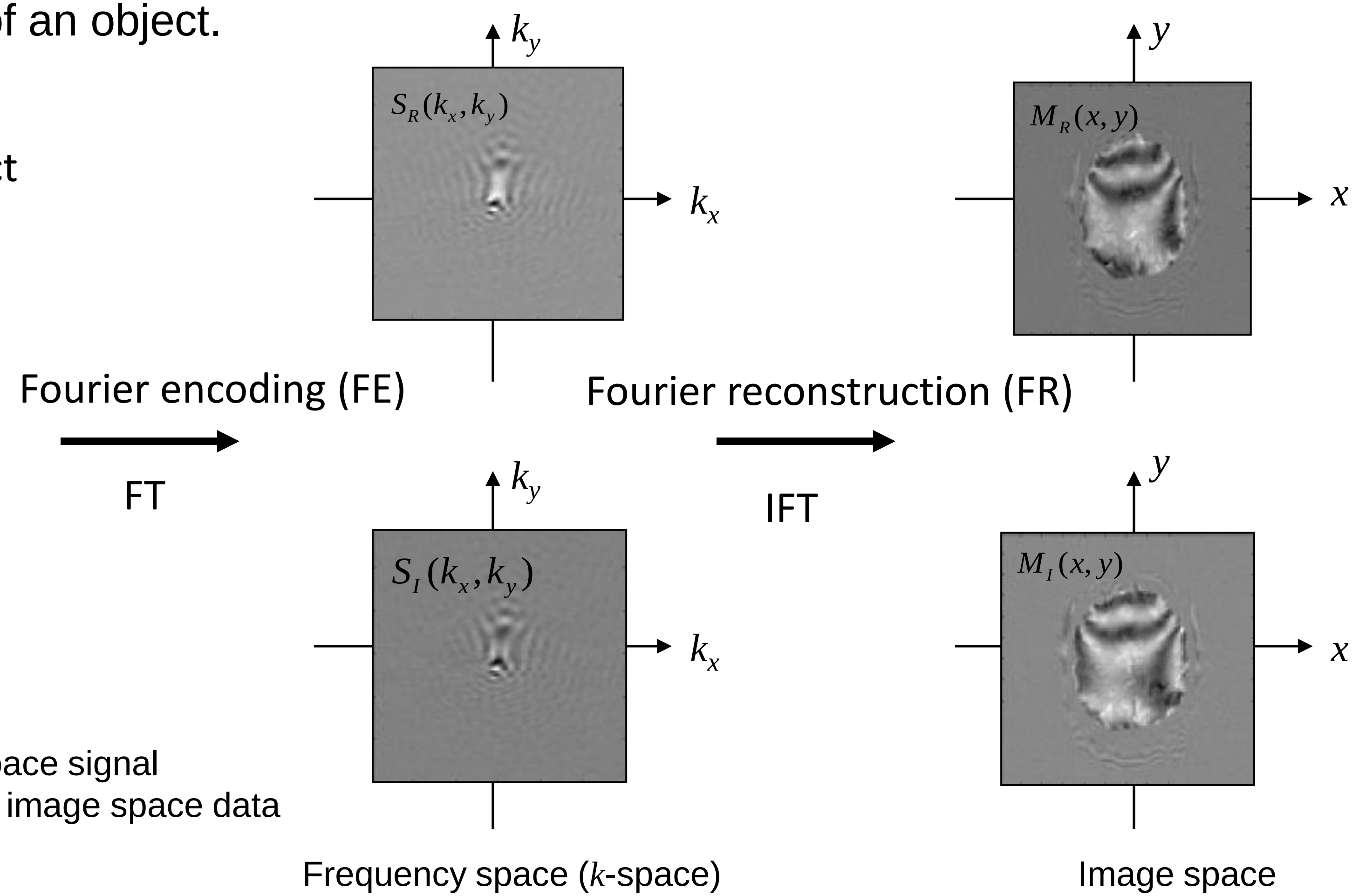
Figure from: www.visualphotos.com

Examining the Statistical Effects of Spatiotemporal Processing

Background – Complex-valued image reconstruction

- In MRI, magnetic field gradients Fourier encode the complex-valued spatial frequencies of an object.





$S(k_x,k_y)$: acquired k-space signal
$M(x,y)$: reconstructed image space data

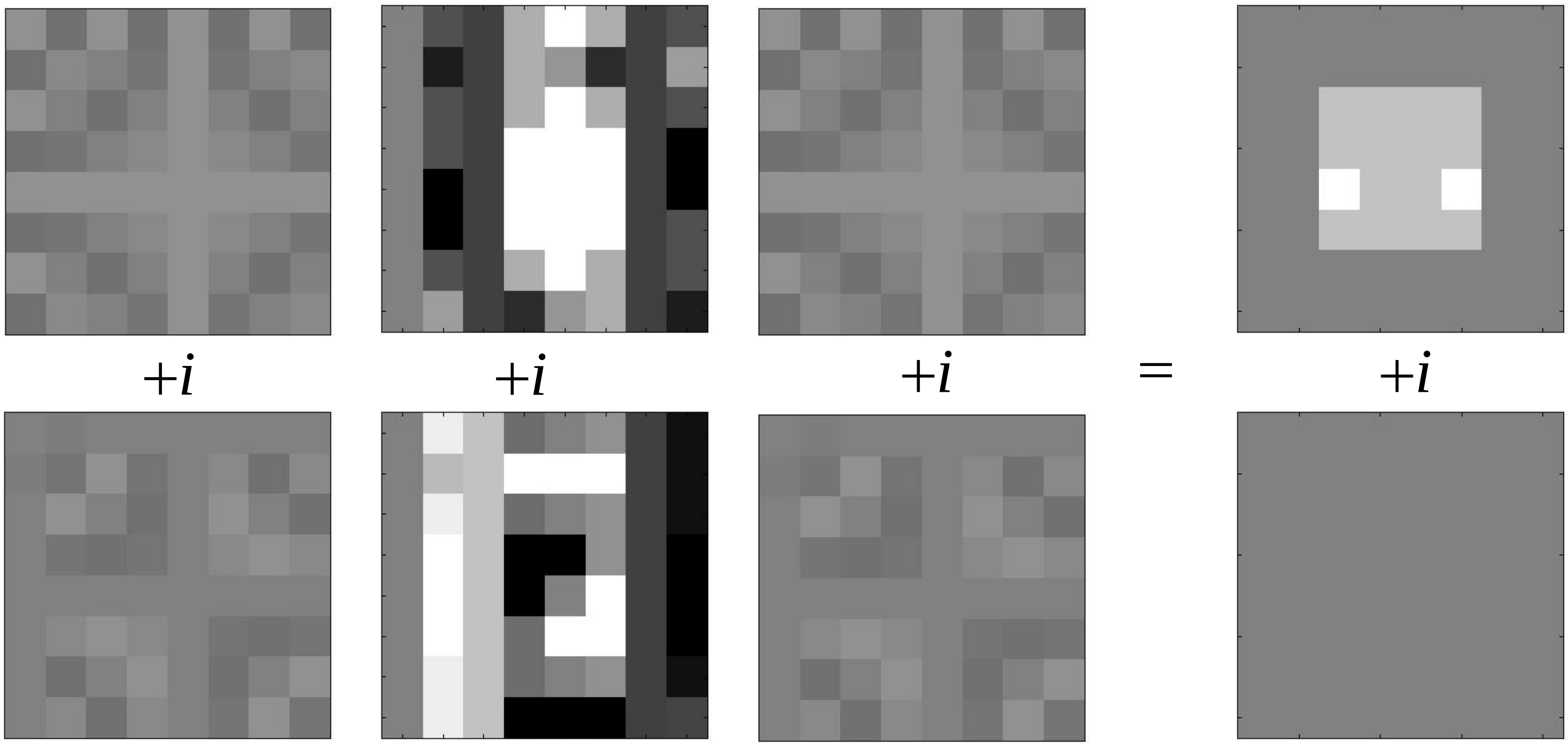
Figure from: www.visualphotos.com

Background – Complex-valued image reconstruction

Complex-valued 2D IFT

$m = n = 8$

$$\left(\Omega_{yR} + i\Omega_{yI}\right) * \left(s_R + is_I\right) * \left(\Omega_{xR} + i\Omega_{xI}\right)^T = \rho_R + i\rho_I$$

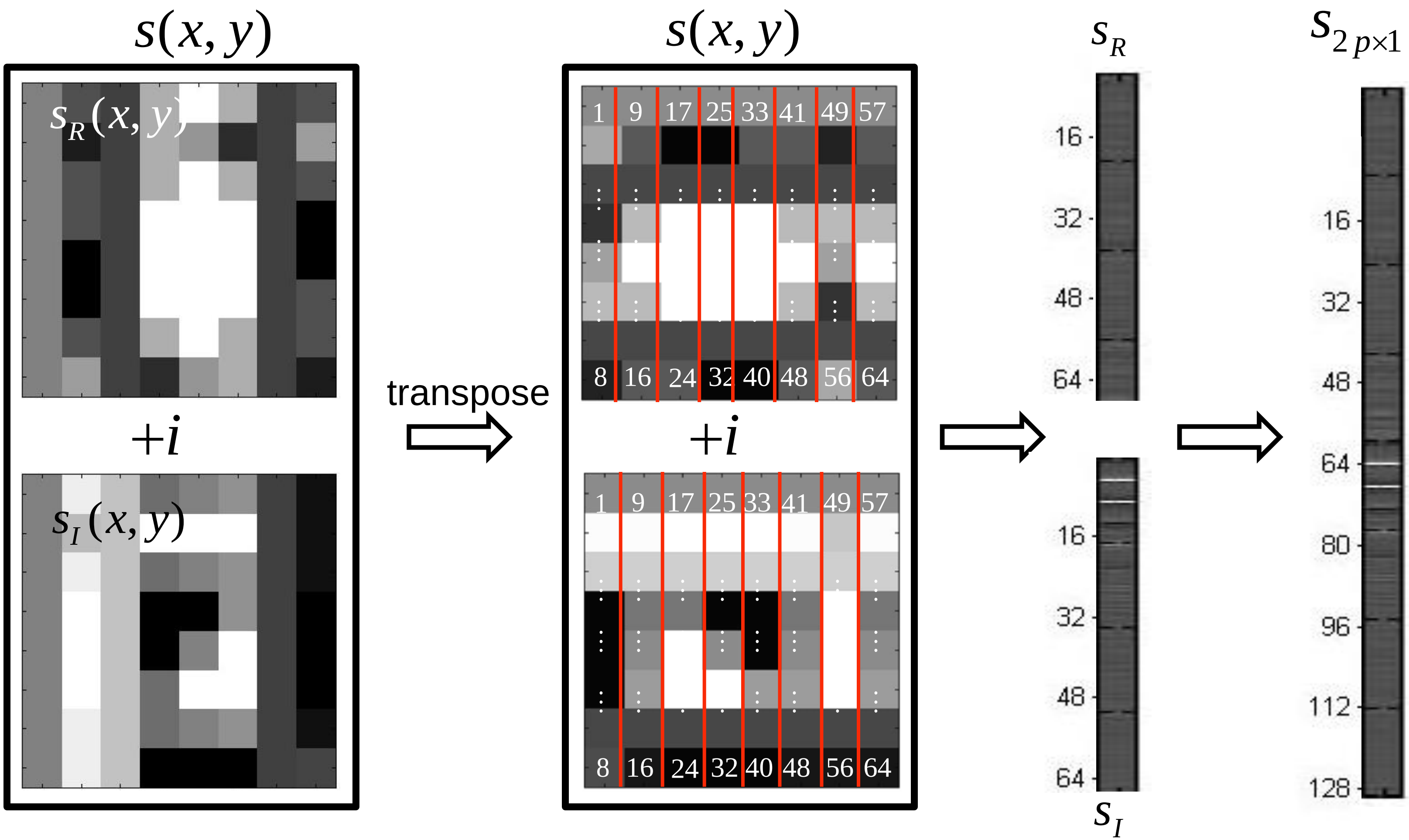


Rowe, Nencka, Hoffman: JNM, 159:361-369, 2007.

Examining the Statistical Effects of Spatiotemporal Processing

Background - Linear complex-valued image reconstruction

- $m \times n$ complex-valued k-space observation can be represented by a $2p$×1 vector



$p = mn$

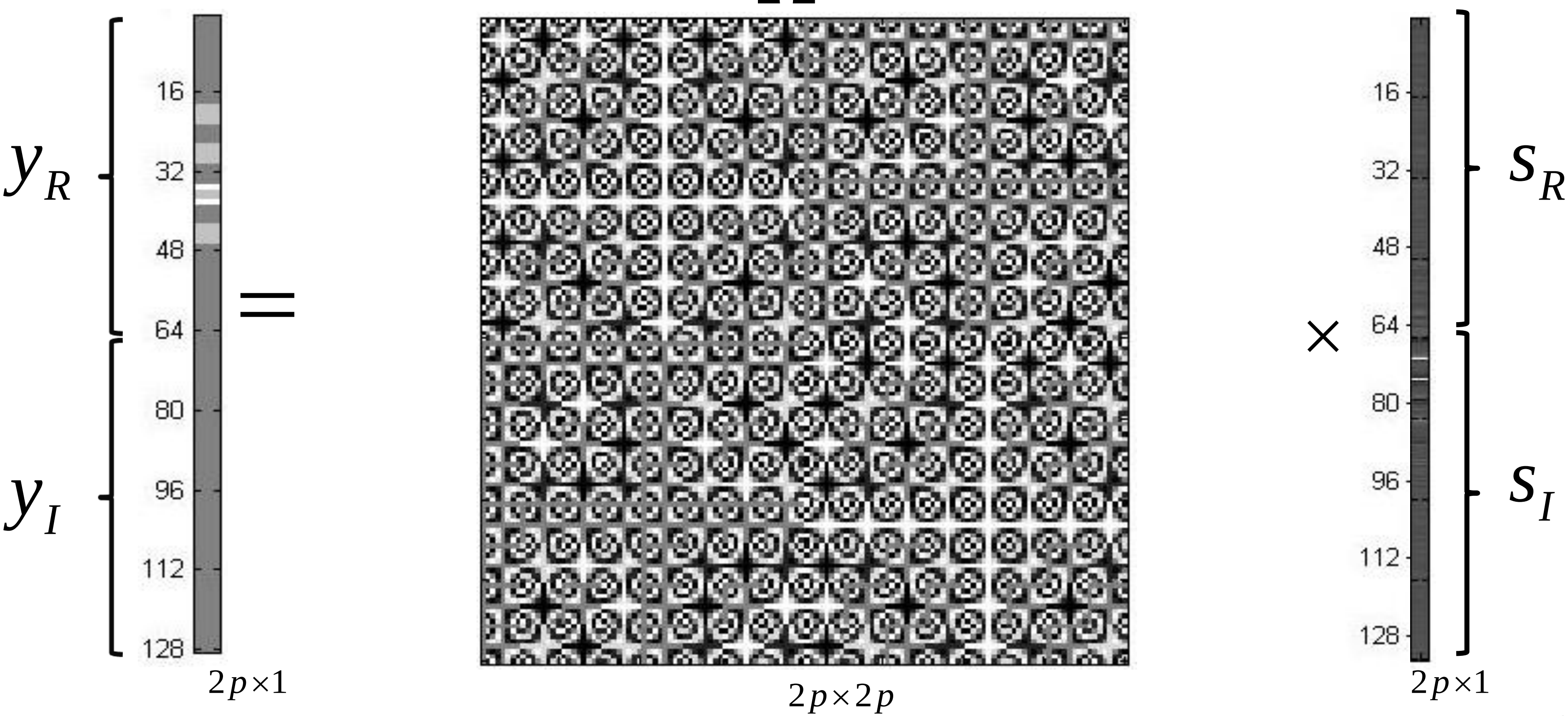
Rowe, Nencka, Hoffman: JNM, 159:361-369, 2007.

Examining the Statistical Effects of Spatiotemporal Processing

Background – Linear complex-valued image reconstruction

$$y = O \times s$$

$$y = \Omega \times s$$



$m = n = 8$

Nencka, Hahn, Rowe: JNSM, 181:268-282, 2009.

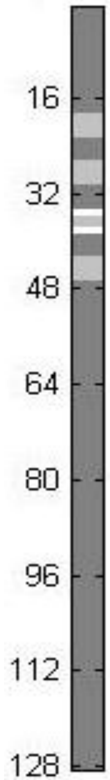
Examining the Statistical Effects of Spatiotemporal Processing

Background – Individual Image Processing

$$y = O \times s$$

$$y = O_I \times \Omega \times O_K \times s$$

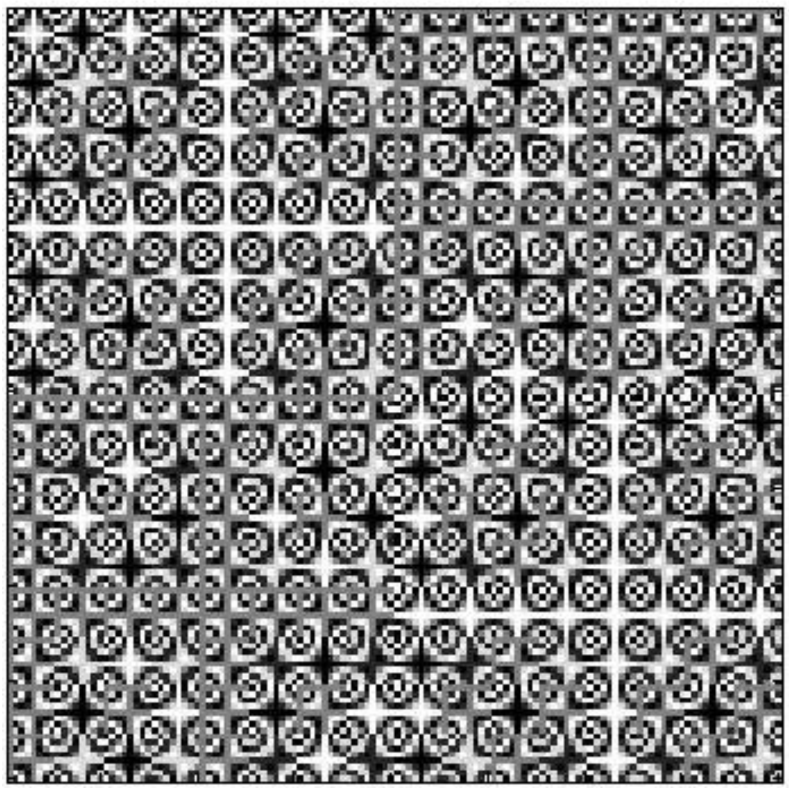
$\begin{bmatrix} y_R \\ y_I \end{bmatrix}$



$2p \times 1$

$= O_I \times$

↓ Image processing



$2p \times 2p$

$\times O_K \times$

↓ k-space processing

$2p \times 1$

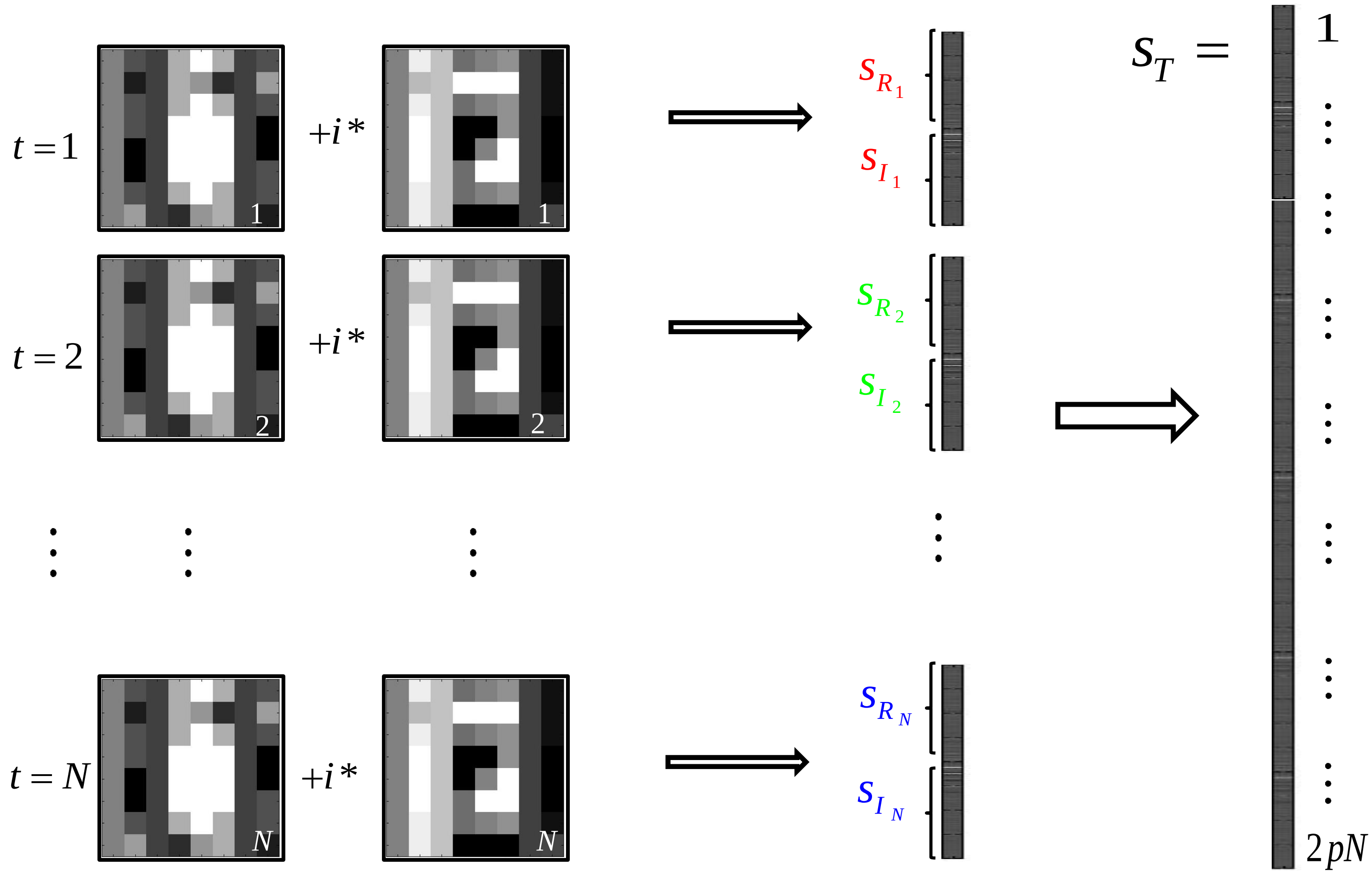
$\begin{bmatrix} s_R \\ s_I \end{bmatrix}$

$m = n = 8$

Nencka, Hahn, Rowe: JNSM, 181:268-282, 2009.

Time Series Analysis Framework

- The observed $m \times n$ k-space arrays in a time series of N points can be vectorized as in individual image processing framework.

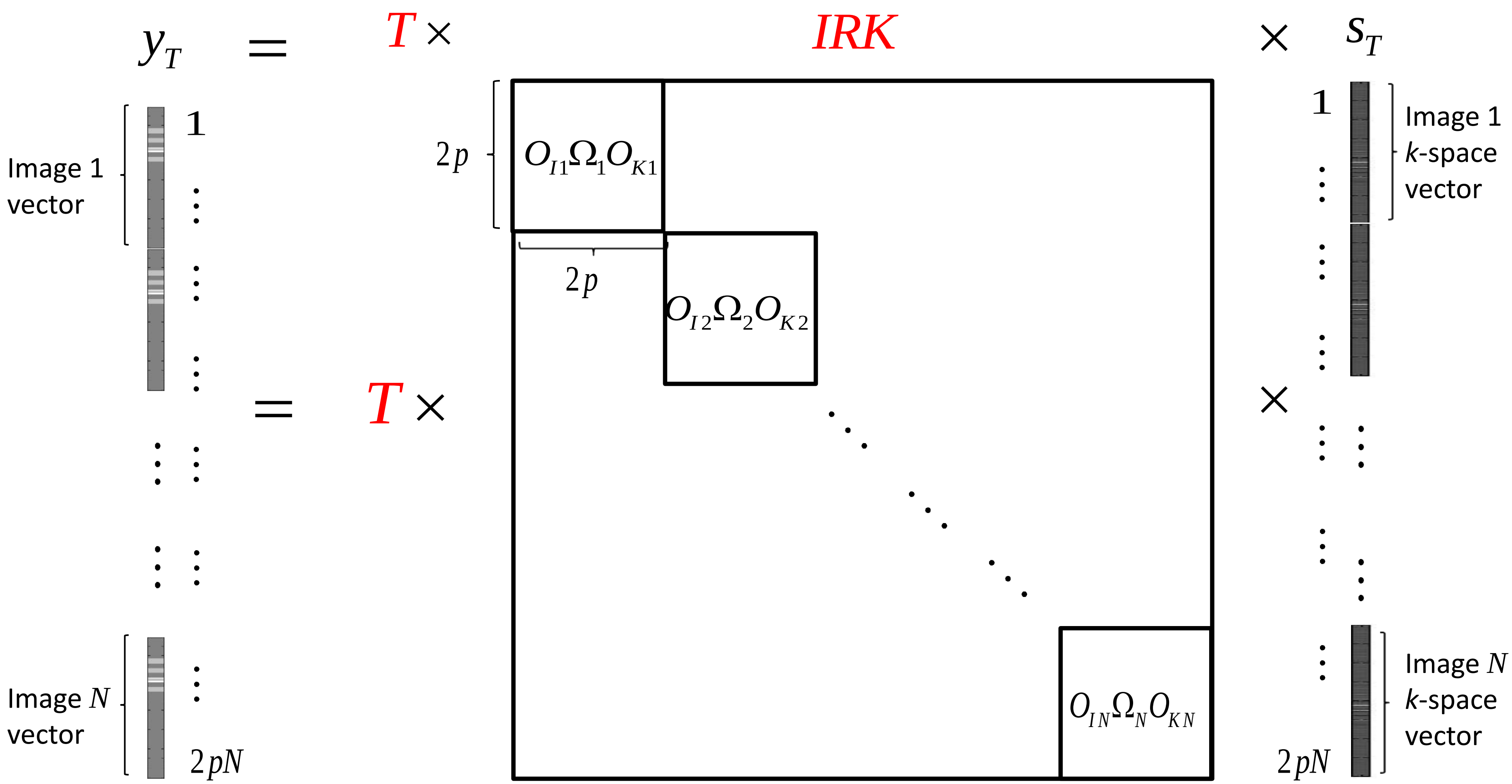


Karaman, Nencka, Rowe: Proc. Intl. Soc. Magn. Reson.Med., 21:2232, Salt Lake City, Utah, USA, 2013.

Examining the Statistical Effects of Spatiotemporal Processing

Time Series Analysis Framework

- The operator, O_T, can then be pre-multiplied by vectorized s_T.



Time Series Analysis Framework

$$y_T = TIRK s_T = O_T s_T$$

How much artificial spatial and/or temporal correlation do we induce by doing that?

Functional Correlations

$$y_T = O_T s_T$$

- Assume $E(s_T) = s_{T_0}$ and $\mathrm{cov}(s_T) = \Gamma$
- Spatiotemporal covariance: $\Sigma = O_T \Gamma O_T^{\,T}$
- Spatiotemporal correlation: $\Sigma_R = D_T^{-1/2} O_T \Gamma O_T^{\,T} D_T^{-1/2}$ $\quad D_T = diag(\Sigma)$
- Σ consists of diagonal blocks of dimension $2p \times 2p$ that contains covariance matrices of individual images.

$\Sigma =$

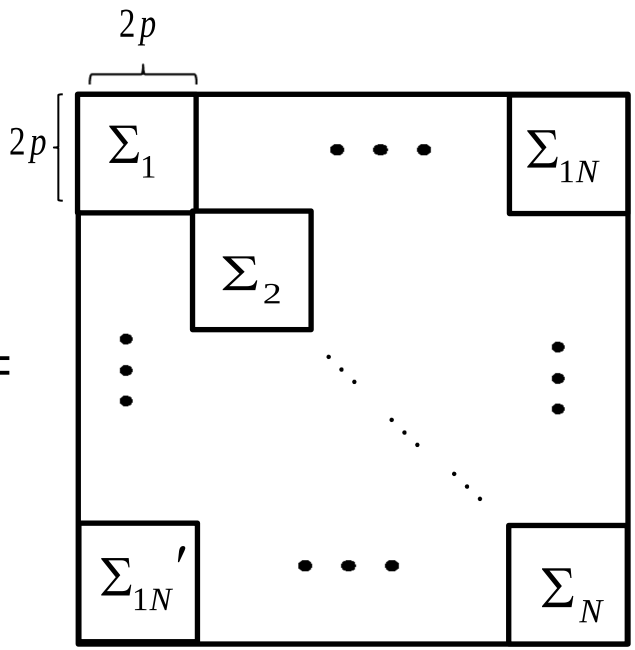


Image time series covariance matrix (Spatial corr's):

$$\Sigma_\rho = \underset{t=1,..,N}{avg}(\Sigma_t) = \begin{pmatrix} \Sigma_{\rho RR} & \Sigma_{\rho RI} \\ \Sigma_{\rho IR} & \Sigma_{\rho II} \end{pmatrix}_{2p \times 2p}$$

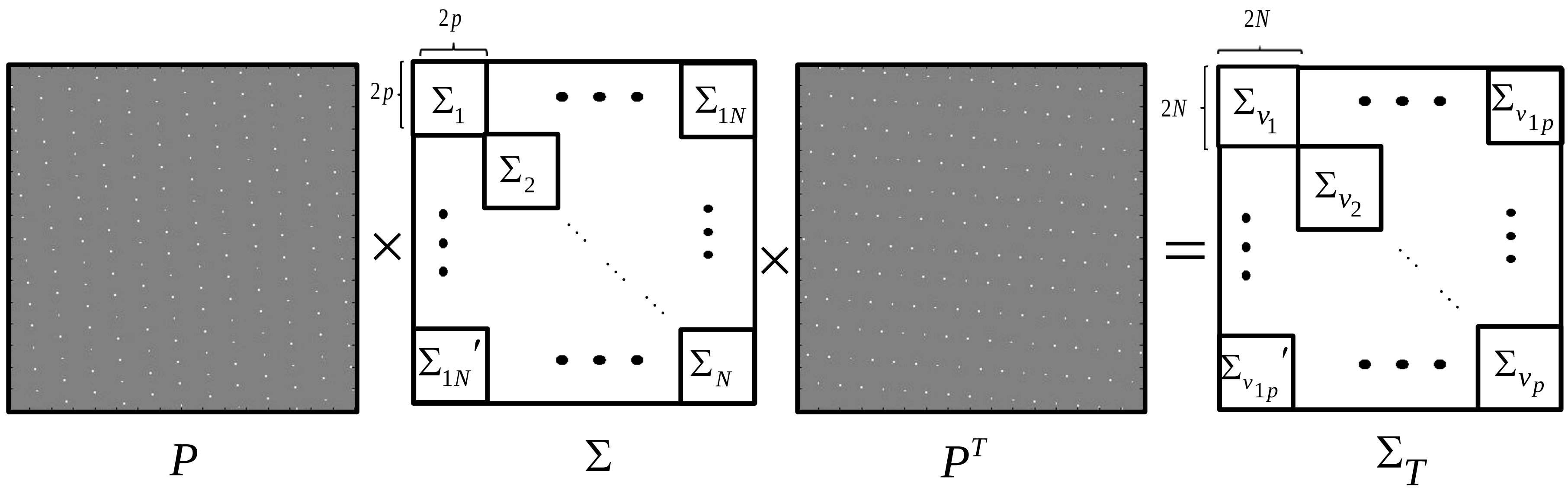
Examining the Statistical Effects of Spatiotemporal Processing

Functional Correlations

$$y_T = O_T s_T$$

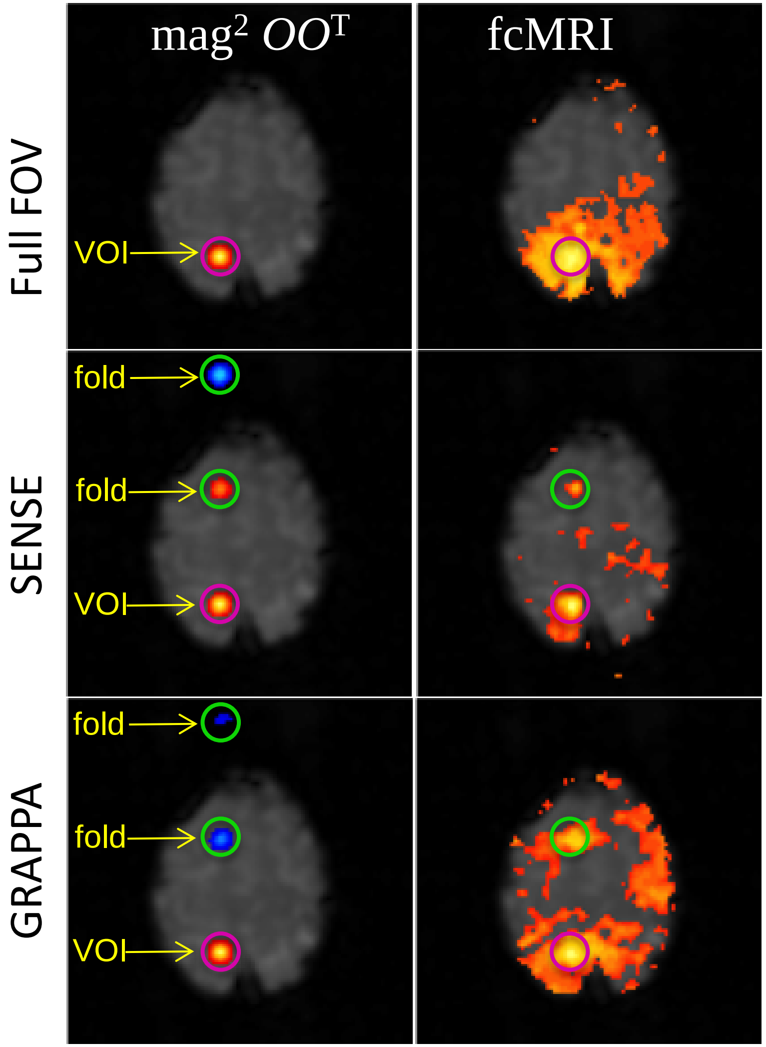
- Assume $E(s_T) = s_{T_0}$ and $\mathrm{cov}(s_T) = \Gamma$
- Spatiotemporal covariance: $\Sigma = O_T \Gamma O_T^{\,T}$
- Spatiotemporal correlation: $\Sigma_R = D_T^{-1/2} O_T \Gamma O_T^{\,T} D_T^{-1/2}$ — $D_T = diag(\Sigma)$
- Σ consists of diagonal blocks of dimension $2p \times 2p$ that contains covariance matrices of individual images.

Voxel time series covariance matrix (Temporal corr's):

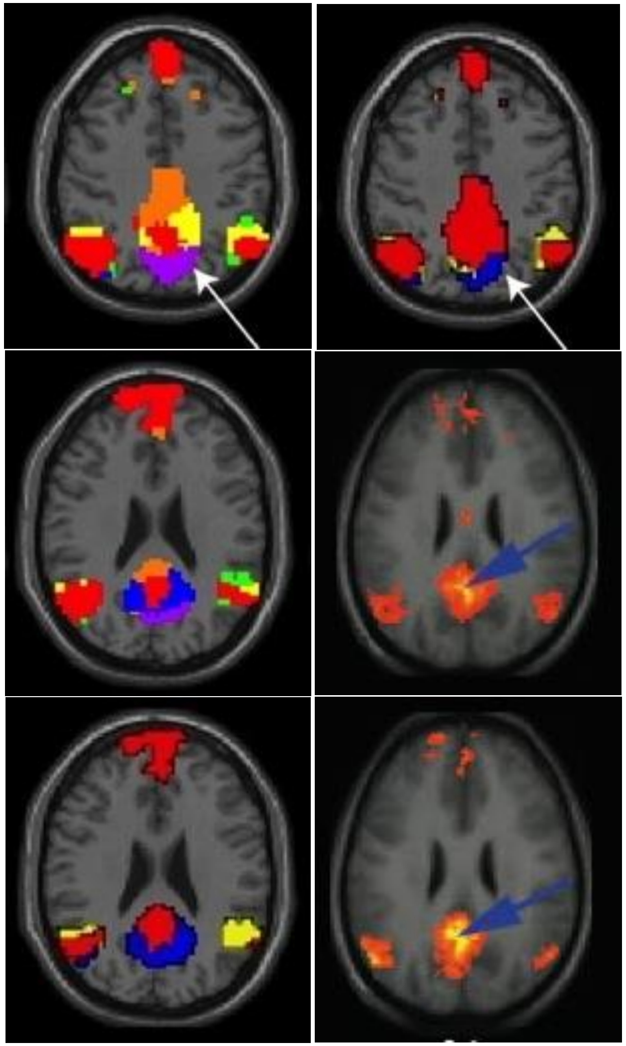


Examining the Statistical Effects of Spatiotemporal Processing

SENSE and GRAPPA Induced Correlations



Bruce, Karaman, Rowe: MRI, 30(8):1143-1166, 2012.
Bruce, Rowe: IEEE, 33(2):495-503, 2014.



Default Mode Network

Number of citations:
PubMed – 754
Google Scholar – 2423

Anderson, JS et al. PNAS 2010;107:20110-20114
Greicus, MD et al. PNAS 2003;100:4637-4642

Examining the Statistical Effects of Spatiotemporal Processing

Theoretical Operator Induced Correlations

- A single slice 96×96 image was considered in a time series of 490 repetitions.
- Data was assumed to be subsampled by an acceleration factor of A=3 with N_C=4 coils.

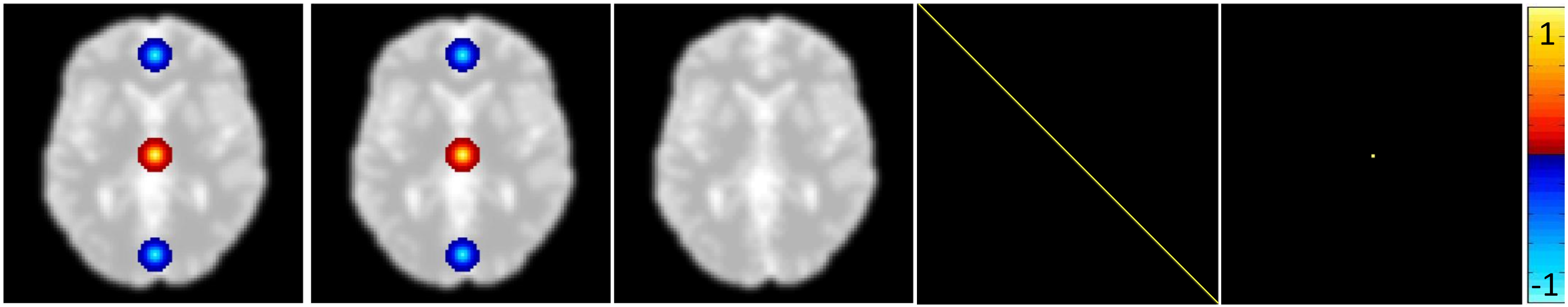
	Smoothing	Temp. Filt.	SENSE Recons.	Initial Voxel Covariance
Case. I:	1	0	1	0
Case. II:	1	0	1	1
Case. III:	1	1	1	0
Case. IV:	1	1	1	1

- Smoothing: Gaussian smoothing with fwhm of 3 pixels.
- Temporal Filtering: Band pass filtering at 0.08 Hz and 0.009 Hz.
- Programs are written in MATLAB on a dual quad-core PC with 48 gigabytes of RAM running Microsoft Windows 7.

Examining the Statistical Effects of Spatiotemporal Processing

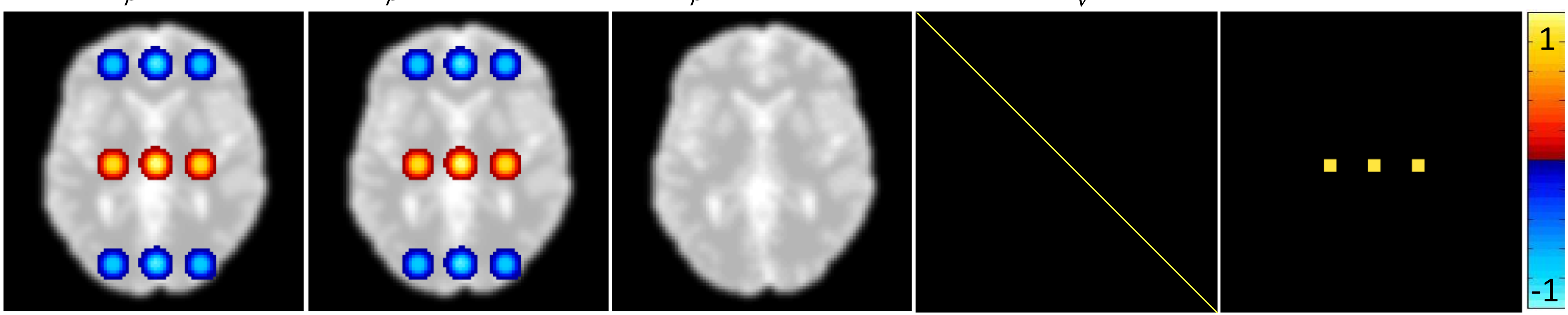
Theoretical Operator Induced Correlations (Center Voxel)

Σ_{R_ρ} (Re/Re) Σ_{R_ρ} (Im/Im) Σ_{R_ρ} (Re/Im) Σ_{R_v} Mask for $\Gamma = I$



Case I (Smoothing:1, Temp. Filt.: 0, SENSE: 1, Initial Vox. Cov.: 0)

Σ_{R_ρ} (Re/Re) Σ_{R_ρ} (Im/Im) Σ_{R_ρ} (Re/Im) Σ_{R_v} Mask for $\Gamma \neq I$

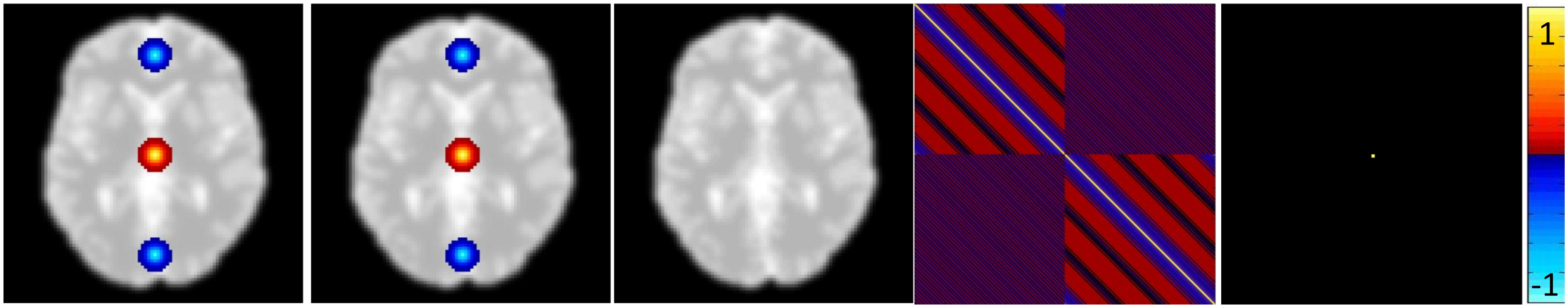


Case II (Smoothing:1, Temp. Filt.: 0, SENSE: 1, Initial Vox. Cov.: 1)

Examining the Statistical Effects of Spatiotemporal Processing

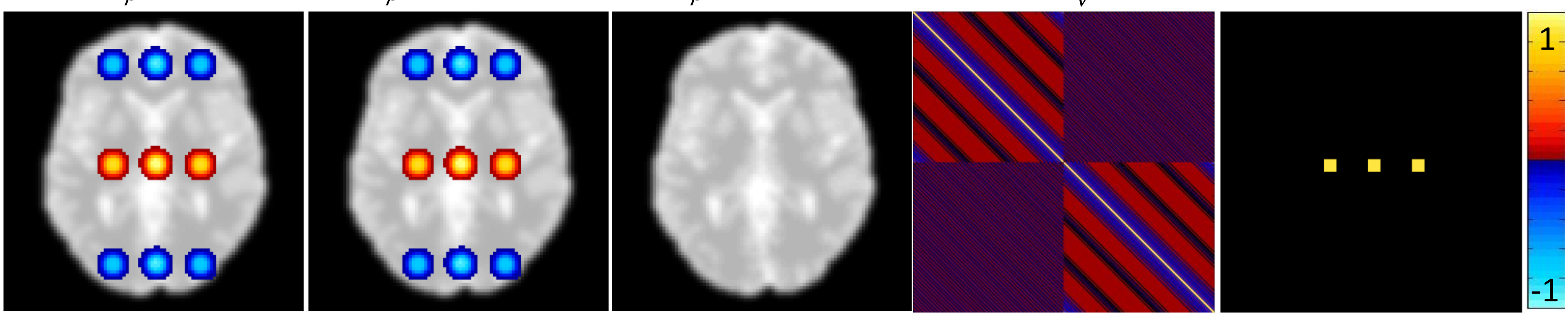
Theoretical Operator Induced Correlations (Center Voxel)

Σ_{R_ρ} (Re/Re) | Σ_{R_ρ} (Im/Im) | Σ_{R_ρ} (Re/Im) | Σ_{R_v} | Mask for $\Gamma = I$



Case III (Smoothing:1, Temp. Filt.: 1, SENSE: 1, Initial Vox. Cov.: 0)

Σ_{R_ρ} (Re/Re) | Σ_{R_ρ} (Im/Im) | Σ_{R_ρ} (Re/Im) | Σ_{R_v} | Mask for $\Gamma \neq I$



Case IV (Smoothing:1, Temp. Filt.: 1, SENSE: 1, Initial Vox. Cov.: 1)

Examining the Statistical Effects of Spatiotemporal Processing

Experimental Illustration – Induced Correlations (Phantom)

- Spherical agar phantom on a 3.0-T GE Signa LX MR scanner.
- 510 TRs from 8 receiver coils.
- $TR = 1$ s., $TE = 45.4$ ms., $\phi = 45^{o}$, FOV = 24 cm, effective echo spacing = 0.816 ms., bandwidth = 125 kHz, 2.5 mm axial slices.
- 490 images from $N_C = 4$ equally spaced coils were utilized for SENSE.
- Data was assumed to be subsampled by an acceleration factor of A=3 .

Processing operations:

- Smoothing: Gaussian smoothing with fwhm of 3 pixels.
- Temporal Filtering: Band pass filtering at 0.08 Hz and 0.009 Hz.

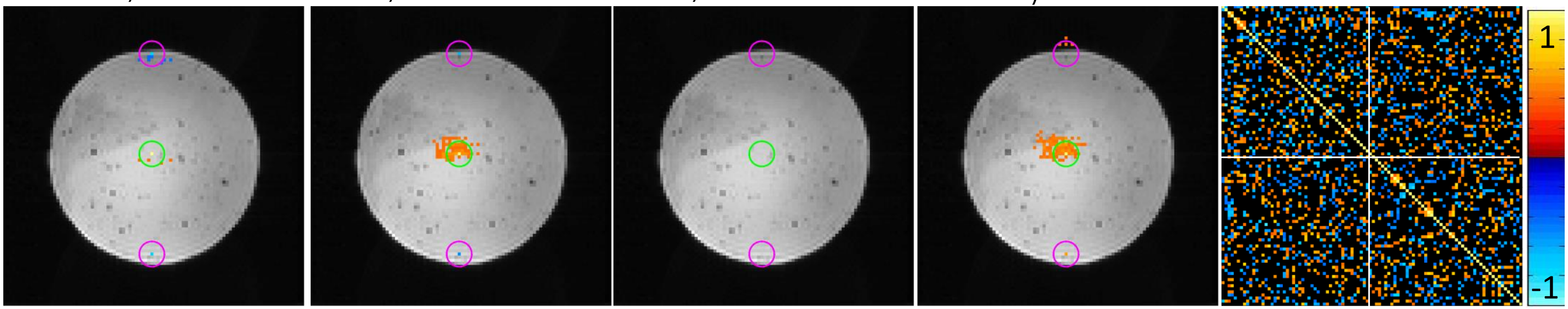
Correlations:

- Spatial correlations were estimated over time series.
- Temporal correlations were estimated over 10 intervals of 49 TRs.

Examining the Statistical Effects of Spatiotemporal Processing

Experimental Illustration – Induced Correlations (Phantom)

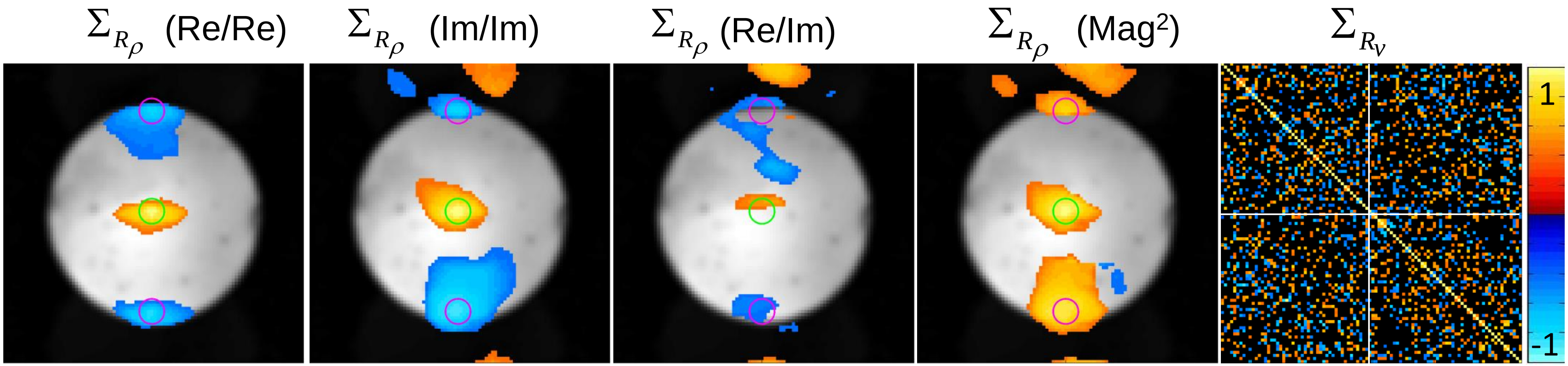
Σ_{R_ρ} (Re/Re) Σ_{R_ρ} (Im/Im) Σ_{R_ρ} (Re/Im) Σ_{R_ρ} (Mag^2) Σ_{R_v}



Smoothing:0, Temp. Filt.: 0, SENSE: 1

Examining the Statistical Effects of Spatiotemporal Processing

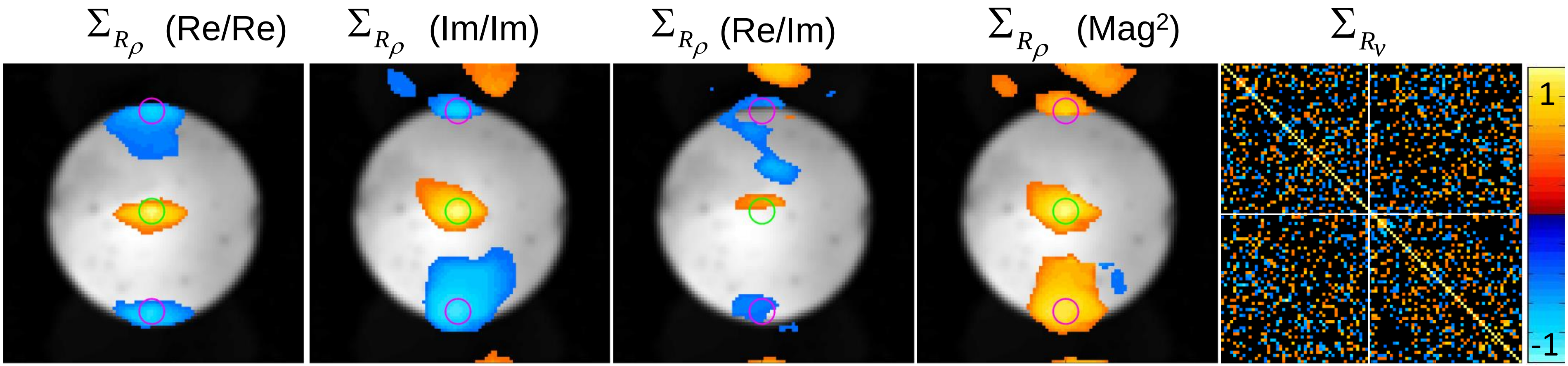
Experimental Illustration – Induced Correlations (Phantom)



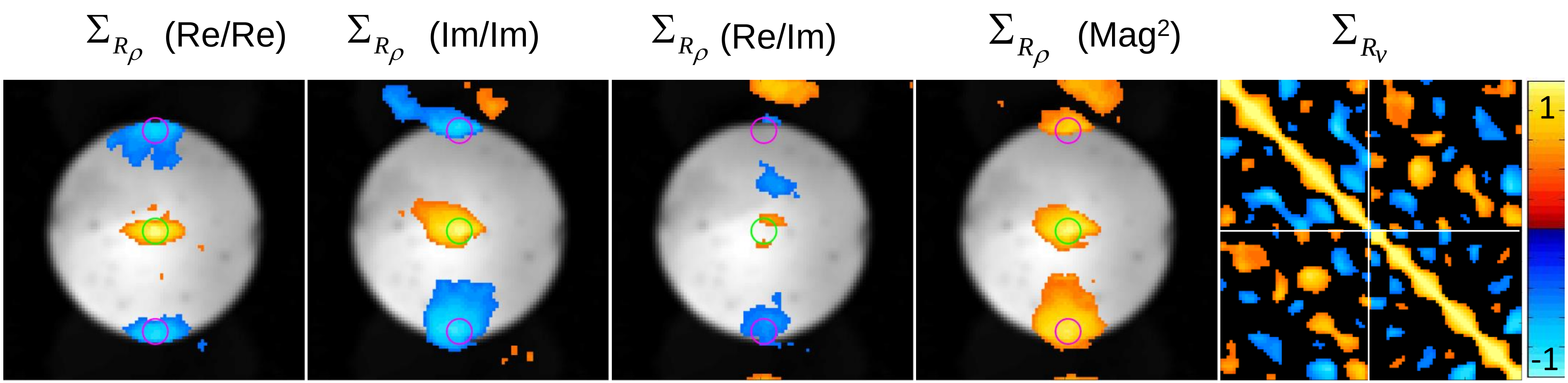
Smoothing:1, Temp. Filt.: 0, SENSE: 1

Examining the Statistical Effects of Spatiotemporal Processing

Experimental Illustration – Induced Correlations (Phantom)



Smoothing:1, Temp. Filt.: 0, SENSE: 1



Smoothing:1, Temp. Filt.: 1, SENSE: 1

Experimental Illustration – Induced Correlations (Human)

- Single subject on a 3.0-T GE Signa LX MR scanner.
- Non-task 96×96 human subject data for 510 TRs from 8 receiver coils.
- $TR = 1$ s., TE = 45.4 ms., $\phi = 45^{o}$, FOV = 24 cm, effective echo spacing = 0.816 ms., bandwidth = 125 kHz, 2.5 mm axial slices.
- 490 images from $N_C = 4$ equally spaced coils were utilized for SENSE.
- Data was assumed to be subsampled by an acceleration factor of A=3 .

<u>Processing operations:</u>

- Smoothing: Gaussian smoothing with fwhm of 3 pixels.
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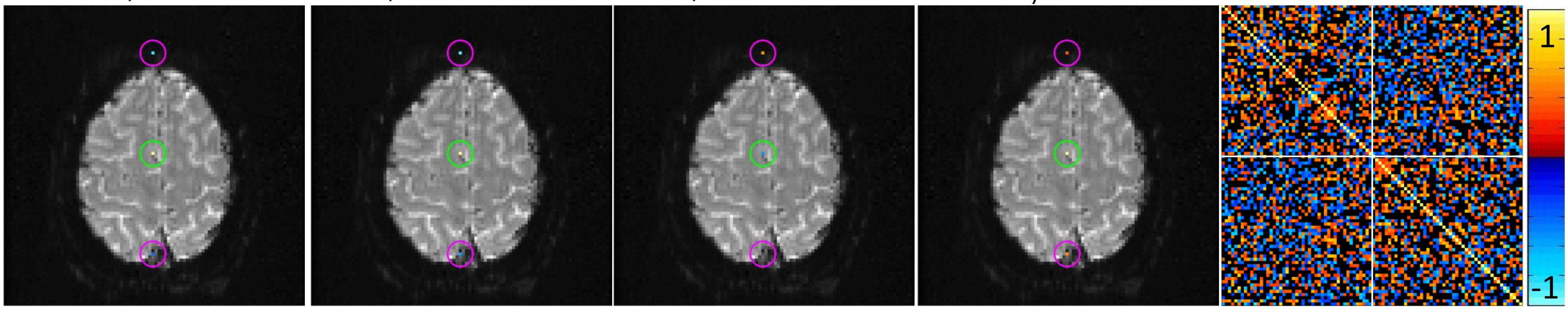
Examining the Statistical Effects of Spatiotemporal Processing

Experimental Illustration – Induced Correlations (Human)

Σ_{R_ρ} (Re/Re) Σ_{R_ρ} (Im/Im) Σ_{R_ρ} (Re/Im) Σ_{R_ρ} (Mag^2) Σ_{R_v}

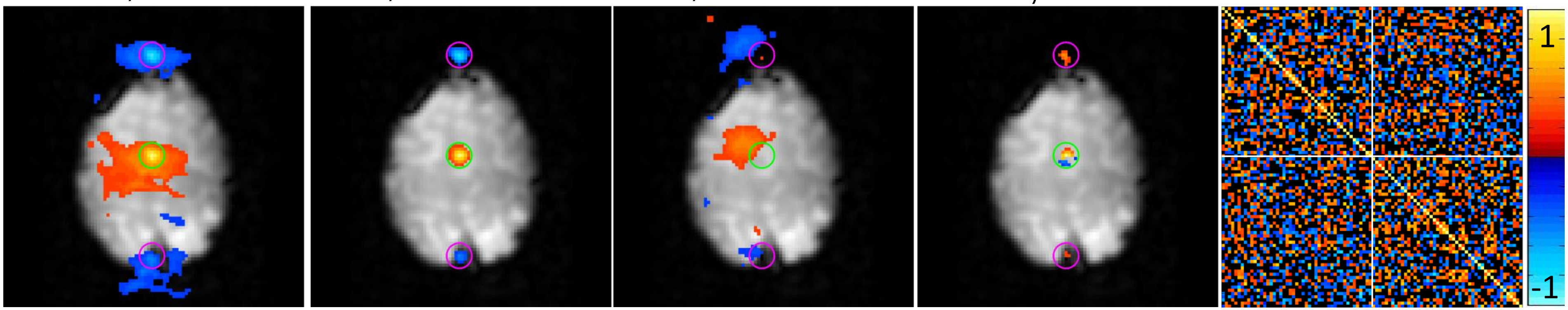


Smoothing:0, Temp. Filt.: 0, SENSE: 1

Examining the Statistical Effects of Spatiotemporal Processing

Experimental Illustration – Induced Correlations (Human)

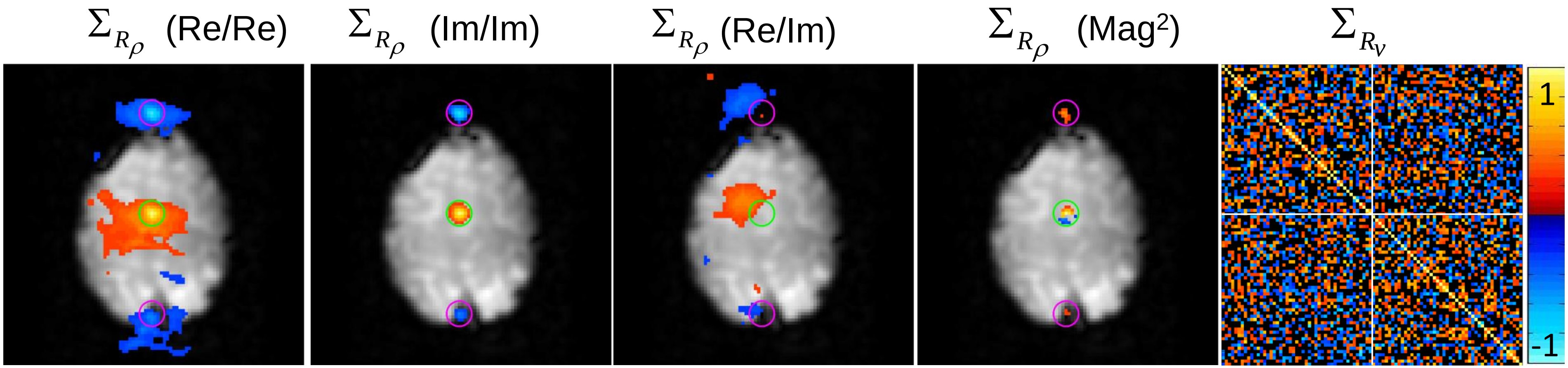
Σ_{R_ρ} (Re/Re) Σ_{R_ρ} (Im/Im) Σ_{R_ρ} (Re/Im) Σ_{R_ρ} (Mag^2) Σ_{R_v}



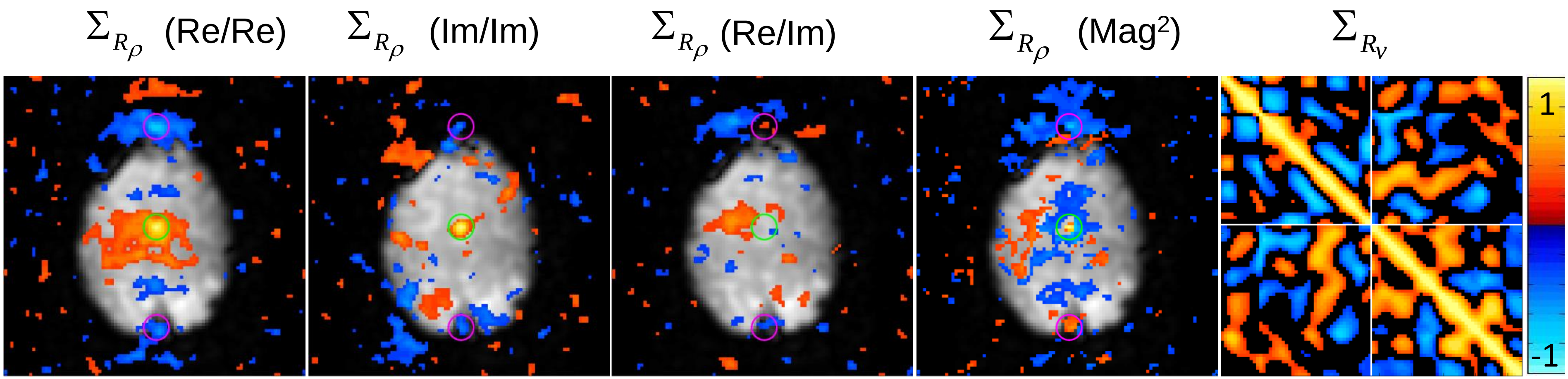
Smoothing:1, Temp. Filt.: 0, SENSE: 1

Examining the Statistical Effects of Spatiotemporal Processing

Experimental Illustration – Induced Correlations (Human)



Smoothing:1, Temp. Filt.: 0, SENSE: 1



Smoothing:1, Temp. Filt.: 1, SENSE: 1

Functional Activations

- Spatial and temporal processing alters the noise properties of the reconstructed and processed fMRI data.

However

- fMRI model assumes independence between voxels:

usually assumed to be $\sigma_j^2 I_2 \otimes I_n$

CV Model: $$\begin{pmatrix} y_{R_j} \\ y_{I_j} \end{pmatrix} = \begin{pmatrix} C_j X_j \beta_j \\ S_j X_j \beta_j \end{pmatrix} + \begin{pmatrix} \eta_{R_j} \\ \eta_{I_j} \end{pmatrix}, \quad \left(\eta_{R_{tj}}, \eta_{I_{tj}}\right)' \sim N\left(0, \Sigma_{v_j}\right)$$

voxel-by-voxel

$C_j : \cos(\theta_j)\, I_n$
$S_j : \sin(\theta_j)\, I_n$

Data processing can corrupt the neuroscientific conclusions drawn from the data if they are unaccounted for.

Rowe and Logan: Neuroimage, 2004; 23(3):1078-1092.

Functional Activations

- Spatial and temporal processing alters the noise properties of the reconstructed and processed fMRI data.

However

- fMRI model assumes independence between voxels:

usually assumed to be $\sigma_j^2 I_n$

MO Model: $$y_{m_j} = X_j \beta_j + \varepsilon_j, \qquad \varepsilon_j \sim N\left(0, \Sigma_{v_j}\right)$$

voxel-by-voxel

Data processing can corrupt the neuroscientific conclusions drawn from the data if they are unaccounted for.

Bandettini, Jesmanowicz, Wong, Hyde: MRM, 1993; 30(2):161-173.

Examining the Statistical Effects of Spatiotemporal Processing

Generalized CV-fMRI Activation Model

- A larger regression model can be developed.

$$\eta \sim N\left(0, \Sigma_T\right)$$

$$y_P = JX\beta + \eta$$

$$\underbrace{\begin{pmatrix} y_{R1} \\ y_{I1} \\ \vdots \\ y_{Rp} \\ y_{Ip} \end{pmatrix}}_{y_P} = \underbrace{\begin{pmatrix} C_1 & 0 & & & 0 \\ 0 & S_1 & & & \\ & & \ddots & & \\ & & & C_p & 0 \\ 0 & & & 0 & S_p \end{pmatrix}}_{J} \underbrace{\begin{pmatrix} X_1 & 0 & & & 0 \\ 0 & X_1 & & & \\ & & \ddots & & \\ & & & X_p & 0 \\ 0 & & & 0 & X_p \end{pmatrix}}_{X} \underbrace{\begin{pmatrix} \beta_1 \\ \beta_1 \\ \vdots \\ \beta_p \\ \beta_p \end{pmatrix}}_{\beta} + \underbrace{\begin{pmatrix} \eta_{1R} \\ \eta_{1I} \\ \vdots \\ \eta_{pR} \\ \eta_{pI} \end{pmatrix}}_{\eta}$$

y_P → $2np \times 1$

J → has θ`s

Examining the Statistical Effects of Spatiotemporal Processing

Generalized MO-fMRI Activation Model

- A larger regression model can be developed.

$$\varepsilon \sim N\left(0, \Sigma_{T_{MO}}\right)$$

$$y_P = X\beta + \varepsilon$$

$$\underbrace{\begin{pmatrix} y_{m1} \\ y_{m2} \\ \vdots \\ y_{mp} \end{pmatrix}}_{y_P} = \underbrace{\begin{pmatrix} X_1 & 0 & & 0 \\ & X_2 & & \\ & & \ddots & \\ 0 & & 0 & X_p \end{pmatrix}}_{X} \underbrace{\begin{pmatrix} \beta_1 \\ \beta_2 \\ \vdots \\ \beta_p \end{pmatrix}}_{\beta} + \underbrace{\begin{pmatrix} \varepsilon_1 \\ \varepsilon_2 \\ \vdots \\ \varepsilon_p \end{pmatrix}}_{\varepsilon}$$

y_P: $np \times 1$

Examining the Statistical Effects of Spatiotemporal Processing

Generalized MO-fMRI Activation Model

$$y_P = X\beta + \varepsilon$$
$$\varepsilon \sim N\left(0, \Sigma_{T_{MO}}\right)$$

- Assume that a "spatial" operation is performed: $\Sigma_{T_{MO}} = \Sigma_\rho \otimes I_n$ (Σ_ρ: $p\times p$ spatial cov. matrix)
- In our model, $X_1 = X_2 = \ldots = X_p = X_v$: $X = I_p \otimes X_v$
- Generalized Least Squares (GLS) solution for the regression coefficients, β:

$$\hat{\beta} = \left[\left(X^T\left(\Sigma_{T_{MO}}\right)^{-1} X\right)^{-1} X^T\left(\Sigma_{T_{MO}}\right)^{-1}\right] y_P$$

$$\hat{\beta} = \left[\left(\left(I_p \otimes X_v\right)^T\left(\Sigma_\rho^{-1} \otimes I_n\right)\left(I_p \otimes X_v\right)\right)^{-1}\left(I_p \otimes X_v\right)^T\left(\Sigma_\rho^{-1} \otimes I_n\right)\right] y_P$$

$$\hat{\beta} = \left[I_p \otimes \left(X_v^T X_v\right)^{-1} X_v^T\right] y_P$$

→ Ordinary Least Squares (OLS) Solution
No gain in estimating the system jointly!

- Multiple comparisons adjustment techniques can be used to account for the spatial processing induced correlations.

Generalized MO-fMRI Activation Model

- Assume that a "spatial and temporal" operation is performed: $\Sigma_{T_{MO}} = \Sigma_{\rho} \otimes \Psi$
- In our model, $X_1 = X_2 = \ldots = X_p = X_v$: $X = I_p \otimes X_v$ — $n \times n$ temporal cov. matrix
- Generalized Least Squares (GLS) solution for the regression coefficients, β:

$$y_P = X\beta + \varepsilon$$

$$\varepsilon \sim N\left(0, \Sigma_{T_{MO}}\right)$$

$$\hat{\beta} = \left[\left(X^T\left(\Sigma_{T_{MO}}\right)^{-1} X\right)^{-1} X^T\left(\Sigma_{T_{MO}}\right)^{-1}\right] y_P$$

$$\hat{\beta} = \left[\left(\left(I_p \otimes X_v\right)^T\left(\Sigma_{\rho}^{-1} \otimes \Psi^{-1}\right)\left(I_p \otimes X_v\right)\right)^{-1}\left(I_p \otimes X_v\right)^T\left(\Sigma_{\rho}^{-1} \otimes \Psi^{-1}\right)\right] y_P$$

$$\hat{\beta} = \left[I_p \otimes \left(\left(X_v^T \Psi^{-1} X_v\right)^{-1} X_v^T \Psi^{-1}\right)\right] y_p$$

Weighted Least Squares (WLS) Solution
No gain in estimating the system jointly!

- WLS can still be used to account for temporal processing induced correlations.

Discussion

- Data processing improves the appearance of the data, however induces correlations of no biological origin.
- Such correlations can increase false negatives and positives in fcMRI analysis.
- AMMUST-*t* framework
  - allows one to precisely quantify artificial correlations induced by data processing,
  - provides tools to draw more accurate and reliable functional connectivity activity results.
- Additional processing operations can be linearized and adopted into the AMMUST-*t* framework.

Thank You!